Review

LABORATORY DIAGNOSTICS OF THE ONCOLOGIC DISEASES IN GASTROENTEROLOGY

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Summary

Studying molecular changes occurring in tumor cells is of major importance. Tumor markers - glycoproteins, glycopeptides, proteins or polypeptides, are all biological products of tumor tissue and are either integrated in the cell membrane or found on the tumor cell surface. So far, scientists have not found an “ideal” tumor marker for any of the malignant diseases in the human body. This means that tumor markers are positive in other diseases too, being related to disturbed function of other organs. The most important role of testing tumor markers remains using them in follow-up and control of therapeutic results.

Key words: tumor markers, gastric-enteral hormones.

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The development of malignant diseases is a process, which passes through the following stages:

- Induction
- Carcinoma in situ
- Invasion
- Metastasising.

Based on long-term observations, there is a reason to assume that the first two stages take 10-20 years. The disease has no clinical manifestation, and changes are not detected in most of the laboratory tests. Deviations from normal ranges are found in the last two stages. Thus, the applicability of laboratory tests in early diagnosing of cancer and screening of risk groups remains debatable.

Nowadays, the main application of laboratory tests is to make an assessment of a patient's status, so as to choose the optimal treatment and for judgment of its effect, as well as for making a prognosis [1].

Basic indices in laboratory diagnostics

These are non-specific laboratory tests, which are performed in all patients, regardless of the diagnostic purpose. Undoubtedly, the first test run in clinical practice is that of erythrocyte sedimentation rate (ESR). Higher values obtained suggest advanced neoplastic process in the phase of invasion or

metastasising.

Anaemic syndrome
It is part of the so-called "haematological stress syndrome", induced by the activation of the macrophages and lymphocytes in response to cell damage, irrespective of the cause: infection, inflammation or neoplasm [2]. The anaemic syndrome is not typical of gastroenterological diseases but is commonly manifested in more than half of the patients with malignant diseases of the gastrointestinal tract. The aetiology of the anaemia is complex, characterized by a well-expressed iron-deficiency syndrome and a low level of transferrine.

Thrombocytosis is found in about 10% of the patients with malignant diseases.

Lymphopenia is a sign of disturbed immune defence in malignant diseases.

Dysproteinemia - hypoalbuminemia with higher concentration of alpha globulines and fibrinogen is a combination, characteristic of most malignant diseases, especially when the liver is concerned.

Dyslipemia - serum cholesterol levels tend to be lower in patients with colorectal carcinoma.

Changes in carbohydrate metabolism (hypo- and hyperglycaemia) are detected in insulinoma and glucagonoma of the exocrine pancreas.

Changes in the bilirubin metabolism in the serum are most common in the following malignant diseases: carcinoma of the major extrahepatal biliary routes; carcinoma of the head of the pancreas; carcinoma of the gallbladder, carcinoma of Vater's papilla.

Changes in the activity of certain enzymes in serum also suggest damage of organs of the gastrointestinal tract, caused by a malignant process. Higher activity of aspartate L-aminotransferase (ASAT) and L-alanine aminotransferase (ALAT) is mostly related to massive liver metastases. Higher concentrations of the serum alkaline phosphatase, gamma glutamil transpeptidase and 5'- nucleotidase suggest malignant tumours, originating from the gastrointestinal tract, liver, pancreas, extra-hepatal biliary routes [3]. In clinical chemical examination of ascites, indices are used which are associated with carcinosis peritonei, the most specific of which are extremely high levels of Lactate dehydrogenase (LDH), and mainly of the isoenzymes LDH 4 and LDH 5.

The diagnostic process is facilitated by finding out tumour markers on the cell surface, using monoclonal antibodies (e.g. cytoceratine, MFG-2, CAE, Ca2 etc.).

Tumor markers

Finding out a definite tumor marker and making it suitable for general use would allow for an early diagnosis, and improve the accuracy of prognosis. Thus, an "ideal" tumor marker for clinical oncology is necessary, with the following features:

- Diagnostic sensitivity and specifity of nearly 100%
- Organ specificity
- A value correlating with the size of the tumor mass
- Cost-effectiveness.

Tumor markers in the serum
Alpha-fetoprotein (AFP)
The identification of AFP in 1963 marked the beginning of the era of tumor markers. Identifying this protein in human fetal serum and detecting its higher levels in patients with primary cancer of the liver (hepatocellular carcinoma [HCC]), opened an exciting perspective of the possible existence of a specific marker for liver carcinoma [4, 5]. Higher levels of AFP are detected in 90-95% of patients with HCC. It is agreed that a value above 500 μg/l is a reliable indicator of HCC [6]. AFP is not significantly high in carcinomas of the stomach, large intestine, biliary routes and pancreas. Its concentration correlates with the size of the tumor, although it can be found in the early stages of the carcinoma [7, 8, 9, 10]. Its level is, to a certain degree, dependent on the tumor cell differentiation [11].
Indications for testing:

- Absolute: suspicion for hepatocellular carcinoma and follow-up of treatment for HCC
- Optional: follow-up and control in patients with liver cirrhosis, with suspected HCC.

Normal values: up to 10-15 μg/l.

Des-gamma carboxyprothrombin (PIVKA II)

Levels of this marker are higher in 91% of the cases with hepatocellular carcinoma, and it is also positive in cases of liver metastases, vitamin K deficiency and chronic active hepatitis. Therefore, its measurement is not routinely administered. Studies on the marker are carried out mainly in the USA, and the test is administered in combination with AFP [12, 13, 14, 15]. It is one of the markers, along with hyperbilirubinemia, ascites, hypoalbuminemia and alkaline phosphatase, used to confirm a prognosis for primary liver carcinoma [J. Bruix, EASL, Barcelona, 2007].

Carcinoembrional antigen (CEA)

It is a typical oncofetal antigen, normally found in lower concentrations in large intestine mucosa. In carcinoma of the large intestine or its liver metastases, its concentrations are over 500 times higher than normal. There is no direct correlation between the size of the tumour and CEA serum concentration values. Measurement of CEA concentrations is used as a subsidiary test in diagnosing colorectal carcinoma. The diagnostic sensitivity depends on the stage of the tumour development. CEA concentrations are tested in diagnosing liver tumours, distant metastases, or its concentration can be followed up postoperatively in patients with the above mentioned conditions [1].

Normal serum values: 1.5-5.0 μg/l.

Carcinoma antigen 19-9 (CA 19-9)

CA 19-9 is a glycolipid, which can be found in the fetal mucosa of the stomach, intestines, liver, pancreas, and meconium. In older patients, minimal quantities are found in the gallbladder, liver and pancreas [1, 16]. In carcinoma of the pancreas, CA 19-9 has a diagnostic sensitivity of 70-95%, and specificity of 72-90%.

There is a correlation between the frequency of elevation of CA 19-9 levels and tumor localisation in pancreas. In cases of tumour of the head of pancreas, the level of the antigen is elevated in 80% of the patients. In cases of tumour of the body or tail of the pancreas, the level of the antigen is higher than normal in 51% of the patients.

There is also a correlation with the size of the tumor: if the tumour is under 3 cm in size, the antigen level is higher than normal in 57% of the patients. When the tumor is larger than 6 cm, the level of the antigen is elevated in 100% of the cases.

There is no correlation with the rate of cell differentiation. CA 19-9 is positive in patients with hepatocellular carcinoma (diagnostic sensitivity of 22-50%), cholangiocellular carcinoma (diagnostic sensitivity of 55-70%.), gastric carcinoma (diagnostic sensitivity of 25-60%) and colorectal carcinoma (diagnostic sensitivity of 25-60%).

It is recommended that CA 19-9 be tested together with CEA in order to increase its diagnostic value. Ca 19-9 is suitable for early detection of postoperative recurrence of carcinoma of the biliary routes and pancreas. It is positive at least 7 months earlier before diagnosing the malignant process with instrumental methods of examination.

Indications for testing:

- Absolute: diagnosis and follow-up of carcinoma of the pancreas, liver and the biliary routes
- Optional: used as an additional marker in diagnosing and follow-up of carcinoma of the large intestine [17].

Normal values: 0-37 U/ml.

Carcinoma antigen 50 (CA 50)

It is used mostly as a second additional marker in cases of pancreatic carcinoma, primary liver carcinoma, carcinoma of the biliary routes, and gastric carcinoma. Its diagnostic value is most useful in cases of carcinoma of the pancreas, preferably in combination with other more specific markers [1].

Normal values: up to 17 U/ml.

Carcinoma antigen 125 (CA 125)

This is a high-molecular lipoprotein, discovered in 1981, which is useful in diagnosing carcinoma of the pancreas. In most of the cases, it is used as a second marker after testing CA 19-9[1]. It is positive in carcinoma of the pancreas carcinoma (diagnostic sensitivity of 45-80%), liver metastases (diagnostic sensitivity of up to 70%), carcinoma of the biliary routes (diagnostic sensitivity of 46%), colorectal carcinoma (diagnostic sensitivity of 10%), gastric carcinoma (diagnostic sensitivity of 14 %).

Normal values: 0 - 35 U/ml.

*Carcinoma antigen 72-4 (*CA 72-4*)*

It is an oncofetal antigen, which is positive in gastric carcinoma. Its diagnostic sensitivity is high: up to 80%. Its diagnostic specifity is also very high, exceeding 95%. Practice has shown that CA 72-4 is more sensitive and specific than CEA and CA 19-9, which makes it a first-choice marker, used in gastric carcinoma control [1]. CA

72-4 is less sensitive (20-40%) in colorectal carcinoma, and in carcinoma of the biliary routes (35-52%). Because of the low diagnostic sensitivity in carcinoma of the esophagus (4-25%), other tumor markers with higher sensitivity should be used.
Normal values-0-4 U/ml.

Tissue polypeptide antigen (TPA)

This is a polypeptide of the cytoceratine type, positive in cases of cell proliferation, which is characteristic of all neoplastic processes. Its specifity is not definitive. It is mostly used as an additional marker in follow-up of carcinomas already diagnosed. TPA is higher in liver carcinomas and carcinoma of the pancreas. Because of its high values in decay and marked cell proliferation, TPA is not suitable for an early diagnosis of malignant diseases. Therefore, it is mainly used in postoperative control [16].
Normal values-up to 60 U/ml.

Gastric-enteral hormones

They are of major importance for the diagnosis of the apudomas-the endocrine tumours of the gastro-intestinal tract and pancreas [18, 19, 21, 22].
Gastrin is a major index in diagnosing gastrinoma.
Vasoactive intestinal polypeptide (VIP) is tested when vipoma is suspected. VIP is a crucial tumor marker in monitoring the effect of treatment. Returning of its concentration in plasma to normal is a proof of successful radical treatment.
Glucagon: values in the serum are higher in glucagonoma [20].
Somatostatin is produced by the D-cells of the Langerhans islets of the pancreas [1] and its concentration is higher in somatostatinoma.
Pancreatic polypeptide- it is found in the tumor tissue and metastases of carcinoid tumours, insulinoma, vipoma, glucagonoma and, relatively rarely, in gastrinoma [1].

Conclusion

The most significant conclusion that we can make and should always consider is that the programs for mass screening are not effective enough in detecting malignant diseases of the gastrointestinal tract, partially excluding colorectal cancer. Tumor markers are of great significance for evaluation of treatment and making a prognosis, since secondary prophylaxis is as significant as an early diagnosis.

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